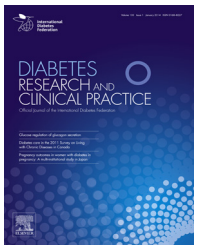
DIABETES RESEARCH AND CLINICAL PRACTICE 106 (2014) 241–246

Contents available at ScienceDirect

Diabetes Research and Clinical Practice

journal homepage: www.elsevier.com/locate/diabres



LDL-apheresis contributes to survival extension and renal function maintenance of severe diabetic nephropathy patients: A retrospective analysis

Eiichi Sato [a,b,*], *Mayuko Amaha* [a], *Mayumi Nomura* [a], *Daisuke Matsumura* [a], *Yoshihiko Ueda* [b], *Tsukasa Nakamura* [a]

[a] *Shin-Matsudo Central General Hospital, Japan*
[b] *Department of Pathology, Dokkyo Medical University, Koshigaya Hospital, Japan*

ARTICLE INFO

Article history:
Received 14 May 2014
Received in revised form
23 July 2014
Accepted 23 August 2014
Available online 3 September 2014

Keywords:
LDL-apheresis
Diabetic nephropathy
Nephrotic syndrome
Retrospective study

ABSTRACT

Aims: Low-density lipoprotein (LDL)-apheresis removes various molecules including LDL/oxidized LDL and inflammatory cytokines and recovers clinical laboratory parameters. It is not yet known whether these advantages of LDL-apheresis improve the prognosis of patients with diabetic nephropathy accompanied by nephrotic syndrome.

Methods: In this study, three groups of patients were retrospectively surveyed in a single center, and followed for approximately 3 years: an LDL-apheresis cohort (LDL-a; $N = 20$); a control cohort meeting the selection criterion of severe proteinuria ≥3 g/24 h (control-All; $N = 55$); and a subgroup of control-All with more severe proteinuria ≥5 g/24 h (control-mSP; $N = 10$), and evaluated the outcomes as survival and renal dysfunction and death/renal dysfunction free rate.

Results: Death/renal dysfunction free rate was significantly higher in LDL-a than control-All ($\chi^2 = 4.50$; $P = 0.03$) and control-mSP ($\chi^2 = 27.68$; $P < 0.001$).

Conclusion: These results suggest the possibilities which LDL-apheresis is considered to contribute to survival extension and renal function maintenance of severe diabetic nephropathy patients.

1. Introduction

Diabetic nephropathy is the most common cause of end-stage renal disease (ESRD) [1,2]. The incidence of end-stage kidney disease requiring chronic hemodialysis caused by diabetic nephropathy has increased rapidly during the last two decades worldwide, and morbidity associated with renal dysfunction involving chronic hemodialysis initiation remains greater than for those without diabetic nephropathy [3,4]. In the pathogenesis of diabetic nephropathy, proteinuria, hyperlipidemia, hyperglycemia, and hypertension are established risk markers observed for progressive renal function loss [5–7]. Several clinical trials have been carried out using drugs such as angiotensin II receptor blockers (ARB) that improve these markers, and the results reported that such drugs conferred improvement in proteinuria and reduction of death and renal dysfunction rates for diabetic nephropathy with proteinuria [8]. However, there is still insufficient data concerning prognosis improvement for severe diabetic nephropathy accompanied by nephrotic syndrome.

* Correspondence to: Division of Nephrology, Department of Internal Medicine, Shin-Matsudo Central General Hospital, Shin-Matsudo 1-380, Matsudo, Chiba Prefecture 270-0034, Japan. Tel.: +81 47 345 1111; fax: +81 47 343 7363.
E-mail address: satou@db4.so-net.ne.jp (E. Sato).

http://dx.doi.org/10.1016/j.diabres.2014.08.012

Some investigators have reported that low-density lipoprotein (LDL)-apheresis is effective in reducing proteinuria excretion in patients with steroid-resistant nephrotic syndrome, focal glomerulosclerosis, and diabetic nephropathy [9,10]. In addition, LDL-apheresis removes various molecules such as oxidized LDL and inflammatory cytokines or chemokine and improves clinical laboratory parameters [11–16], and may reduce renal lesions. We found that LDL-apheresis reduced excretion of podocytes [17], which have a key role in maintaining the integrity of the glomerular filtration barrier [18–20]. These results suggest that the effects of LDL-apheresis are exerted by removal of oxidative/inflammatory molecules and modulation of the inflammatory cascade in the glomerulus, and that it is a potentially effective treatment for diabetic nephropathy with severe proteinuria [17]. It is unknown whether these advantages of LDL-apheresis improve prognosis in terms of mortality or renal dysfunction. The purpose of the present study is to estimate, by means of a retrospective review, the prognosis of diabetic nephropathy with severe proteinuria treated with LDL-apheresis therapy.

1.1. Subjects

The present study is a single-center, retrospective review of diabetic nephropathy patients, consisting of an LDL-apheresis cohort and a control cohort with one subgroup. The LDL-apheresis cohort (LDL-a) is composed of all patients who underwent LDL-apheresis therapy at Shin-Matsudo Central General Hospital, Chiba, Japan prior to 2010 ($N = 20$). The control cohort is composed of all patients at the same hospital who met the inclusion criteria of severe proteinuria $\geq$3 g/24 h from 2008 to 2010 and who were traceable (control-All; $N = 55$); a subgroup of the control cohort comprises the patients in control-All with severe proteinuria $\geq$5 g/24 h (control-mSP; $N = 10$) near to that of LDL-a.

2. Methods

2.1. Diagnosis criteria of diabetic nephropathy

Diabetic nephropathy was diagnosed based on the presence of following diabetic lesions: glomerulosclerosis such as nodular or diffuse (mesangial expansion), hyalinization of the renal arterioles, linear deposits of IgG in the glomerular basement membrane, and diffuse thickening of the glomerular basement on electron microscopy. If there is no renal biopsy data of diabetic lesions, as a substitute by evaluation of clinical laboratory tests: clinical syndrome characterized by persistent albuminuria (>300 mg/24 h) (also referred to as macroalbuminuria or proteinuria), a steady decline in glomerular filtration rate (GFR), and elevated blood pressure [21].

2.2. Clinical parameters and laboratory measurements

Body mass index was calculated as body weight (in kilograms) divided by height (in meters) squared. Hypertension was defined according to WHO criteria (systolic blood pressure [BP] > 160 mmHg and/or diastolic BP > 95 mmHg, or on antihypertensive treatment at baseline). Hypercholesterolemia was defined according to the criteria total cholesterol >220 mg/dL and LDL-cholesterol >140 mg/dL. Stroke was defined as a reported medical history of cerebral infarction or cerebral hemorrhage. Coronary artery disease (CAD) was defined as a reported history of myocardial infarction, angina, percutaneous coronary intervention, or coronary artery bypass graft. Retinopathy and neuropathy were determined from the reported medical history.

Samples of blood and urine taken at routine clinical checkups were analyzed at baseline for creatinine, total protein, LDL-cholesterol, and HbA1c and for protein and liver-type fatty acid binding protein (L-FABP), respectively.

2.3. Outcomes assessment

Baseline for LDL-a and the control cohorts is defined as the day of starting LDL-apheresis therapy or meeting the inclusion criteria, respectively. Surveillance for major events included screening hospitalization history until 3 years from baseline.

A major event was defined as any incident of stroke, CAD, renal dysfunction, or death. Renal dysfunction was defined as doubling of serum creatinine concentration, chronic hemodialysis initiation, or renal transplantation [8]. Doubling of serum creatinine concentration was defined as the first serum creatinine concentration that was twice the baseline, as confirmed by a second serum creatinine concentration obtained at about 3 months after the initial doubling.

2.4. LDL-apheresis

LDL-apheresis was performed using hollow polysulfone fibers (Sulflux; Kaneka Co. Ltd., Osaka, Japan) as the plasma separator and a dextran sulfate cellulose column (Liposorber; Kaneka Co. Ltd., Osaka, Japan) as the LDL absorber. About 3000 to 4000 mL of plasma (60 mL/kg body weight) was treated for 3 h in each apheresis session [9]. LDL-apheresis was performed in series twice a week for 3–6 weeks (6–12 times per patient).

2.5. Statistical analysis

Data are expressed as the mean $\pm$ SD. Differences in baseline characteristics between two cohorts were evaluated by the chi-square test, or Fisher's exact test for categorical variables or Student's t test for continuous variables. Survival, major event free, renal dysfunction free, and death/renal dysfunction free rates for the cohorts were estimated by the Kaplan–Meier method and analyzed by log-rank tests [22]. Prognostic factors of severe diabetic nephropathy were estimated by logistic regression analysis. Statistical analyses were performed using SPSS version 16.0.

3. Results

3.1. Characteristics of each cohort

Baseline characteristics of LDL-a and the control cohorts are listed in Table 1. Disease severity parameters such as eGFR (35.1 ± 17.7 mL/min/1.73 m^2 vs. 48.6 ± 26.6 mL/min/1.73 m^2; $P = 0.04$), total protein (3.9 ± 0.3 g/dL vs. 6.7 ± 0.7 g/dL; $P < 0.001$), LDL cholesterol (227.1 ± 33.0 mg/dL vs.

Table 1 – Baseline characteristics.

	LDL-a	Control			
	(N = 20)	All (N = 55)	P Value	mSP (N = 10)	P Value
Male/female	15/5	35/20	0.4	5/5	0.2
Age (years)	59.3 ± 13.8	65.9 ± 12.1	0.05	62.4 ± 14.1	0.6
Diabetes duration (years)	21.3 ± 10.0	14.0 ± 8.5	0.004	17.7 ± 13.8	0.5
Follow-up (years)	2.7 ± 0.4	2.5 ± 0.7	0.2	2.8 ± 0.4	0.6
BMI (kg/m^2)	26.9 ± 3.4	24.4 ± 4.4	0.03	25.3 ± 5.5	0.4
Serum creatinine (mol/L)	170.6 ± 81.3	142.3 ± 126.4	0.4	198.0 ± 155.6	0.5
eGFR (mL/min/1.73 m^2)	35.1 ± 17.7	48.6 ± 26.6	0.04	36.7 ± 32.2	0.9
Total protein (g/dL)	3.9 ± 0.3	6.7 ± 0.7	<0.001	6.3 ± 0.8	<0.001
LDL-cholesterol (mg/dL)	227.1 ± 33.0	157.1 ± 69.1	<0.001	165.8 ± 61.8	0.002
HbA1c (%)	7.6 ± 0.8	7.4 ± 2.0	0.7	6.8 ± 2.3	0.2
Proteinuria (g/24 h)	10.5 ± 2.1	3.7 ± 1.9	<0.001	6.8 ± 2.9	<0.001
L-FABP (urinary, μg/gCr)	179.1 ± 84.0	100.5 ± 57.1	<0.001	129.9 ± 64.7	0.1
Stroke (history; *n*, %)	12, 60	14, 25	<0.001	3, 30	0.1
CAD (history; *n*, %)	14, 70	9, 16	<0.001	4, 40	0.1
Hypertension (*n*, %)	14, 70	42, 76	0.6	9, 90	0.2
Hypercholesterolemia (*n*, %)	20, 100	33, 60	0.03	9, 90	0.3
Retinopathy (*n*, %)	15, 75	33, 60	0.2	7, 70	0.6
Neuropathy (*n*, %)	15, 75	15, 27	<0.001	3, 30	0.02
Heart failure (*n*, %)	14, 70	9, 16	<0.001	5, 50	0.3
ACE inhibitor (*n*, %)	3, 15	8, 15	0.6	2, 20	0.8
ARB (*n*, %)	14, 70	27, 49	0.1	6, 60	0.4
Statin (*n*, %)	20, 100	18, 33	<0.001	6, 60	0.008
Insulin (*n*, %)	8, 40	11, 20	0.08	2, 20	0.3

157.1 ± 69.1 mg/dL; $P < 0.001$), proteinuria (10.5 ± 2.1 g/24 h vs. 3.7 ± 1.9 g/24 h; $P < 0.001$), and L-FABP (179.1 ± 84.0 μg/gCr vs. 100.5 ± 57.1 μg/gCr; $P < 0.001$) were significantly more severe in LDL-a than control-All; however, there was no difference in serum creatinine (170.6 ± 81.3 mol/L vs. 142.3 ± 126.4 mol/L; $P = 0.35$). Total protein (6.3 ± 0.8 g/dL; $P < 0.001$), LDL cholesterol (165.8 ± 61.8 mg/dL; $P = 0.002$), and proteinuria (6.8 ± 2.9 g/24 h, $P < 0.001$) were significantly more severe in LDL-a than control-mSP. In LDL-a cohort, LDL cholesterol levels were significantly decreased after LDL-apheresis treatment (from base line: 227.1 ± 33.0 mg/dL to after: 88.0 ± 15.5 mg/dL; $P < 0.001$) and restored to normal range.

Life-threatening history or concomitant diseases such as stroke ($P < 0.001$), coronary artery disease (CAD; $P < 0.001$), and heart failure ($P < 0.001$) were significantly higher in LDL-a than control-All; however, there were no differences in life-threatening history or concomitant diseases between LDL-a and control-mSP.

The frequency of use of anti-hypertension drugs, ACE inhibitors and ARB, and insulin were almost the same in each cohort. On the other hand, the frequency of statin use was significantly higher in LDL-a (100%) than control-All (33%; $P < 0.001$) and control-mSP (60%; $P = 0.008$).

3.2. *Major events*

Major events for LDL-a and the control cohorts are listed in Table 2. Major events were observed for 14 patients (70%) in LDL-a, 35 patients (64%) in control-All, and 10 patients (100%) in control-mSP. Incidence of CAD was significantly higher in

Table 2 – List of major events.

	LDL-a		Control					
	(N = 20)		All (N = 55)		P value	mSP (N = 10)		P value
Stroke (*n*, %)	5	(25)	6	(11)	0.1	2	(20)	0.6
CAD (*n*, %)	11	(55)	10	(18)	0.002	2	(20)	0.07
Renal dysfunction (*n*, %)	5	(25)	23	(42)	0.18	10	(100)	<0.001
Creatinine doubling (*n*, %)	5	(25)	19	(35)	0.4	9	(90)	0.001
Dialysis initiation (*n*, %)	5	(25)	16	(29)	0.7	8	(80)	0.006
Death (*n*, %)	1	(5)	15	(27)	0.03	3	(30)	0.1
<Cause of death>								
Stroke			2					
AMI	1		1					
Heart failure			6			1		
Renal failure			2					
Infection			1			1		
Other			3			1		
Event-free (*n*, %)	6	(30)	20	(36)	0.61	0	(0)	0.07

LDL-a than control-All ($P = 0.002$). Mortality was significantly higher ($P = 0.03$) in control-All ($N = 15$; 27%) than LDL-a ($N = 1$; 5%). The most common cause of death in control-All was heart failure, followed by stroke and renal failure. In the renal dysfunction component, incidence of serum creatinine doubling and chronic hemodialysis initiation were significantly higher in control-All than in LDL-a ($P = 0.001$ and $P = 0.006$, respectively).

3.3. *Outcome Analysis*

Survival, renal dysfunction free, death/renal dysfunction free, and major event free rates were estimated by the Kaplan–Meier method and analyzed by log-rank tests. The survival rate was significantly higher in LDL-a than control-All ($\chi^2 = 4.05$ [$P = 0.04$] vs. $\chi^2 = 2.72$ [$P = 0.1$] at 2 years follow-up) (Fig. 1); however, there was no significant difference compared with control-mSP ($\chi^2 = 2.83$; $P = 0.09$) (Fig. 1). The renal dysfunction free rate was significantly higher in LDL-a than control-mSP ($\chi^2 = 28.4$ [$P < 0.001$] vs. $\chi^2 = 30.5$ [$P < 0.001$] at 2 years follow-up) (Fig. 2). There was no significant difference between LDL-a and control-All ($\chi^2 = 3.00$; $P = 0.08$), but a difference was observed at 2 years follow-up ($\chi^2 = 7.26$; $P = 0.007$). The death/renal dysfunction free rate was also significantly higher in LDL-a than control-All ($\chi^2 = 4.50$ [$P = 0.03$] vs. $\chi^2 = 6.91$ [$P = 0.009$] at 2 years follow-up); furthermore, there was a significant difference between LDL-a and control-mSP ($\chi^2 = 28.02$ [$P < 0.001$] vs. $\chi^2 = 27.68$ [$P < 0.001$] at 2 years follow-up) (Fig. 3). On the other hand, the major event free rate showed no significant difference between LDL-a and control-All ($\chi^2 = 0.43$; $P = 0.5$) (figure not shown).

To estimate the independent prognostic factors of severe diabetic nephropathy, baseline variables were compared for death, renal dysfunction, and death/renal dysfunction in control-All. Age, BMI, serum creatinine, total protein, and LDL-cholesterol were identified as candidates, and LDL-cholesterol was finally estimated by multiple logistic regression analysis as the common independent prognostic factor for death (OR, 0.96; 95% CI [0.93–1.00]; $P = 0.03$), renal dysfunction (OR, 0.93; 95% CI [0.88–0.99]; $P = 0.03$), and death/renal dysfunction (OR, 0.94; 95% CI [0.88–1.00]; $P = 0.04$) (Table 3). In addition, total protein was also an independent prognostic factor for death/renal dysfunction (OR, 50.0; 95% CI [2.52–989.8]; $P = 0.01$). In order to examine the influence for the prognosis of statins having an LDL-cholesterol lowering effect, control-All was divided into two groups of patients who met the respective inclusion criteria of with or without the initiation of statin therapy, and survival and death/renal dysfunction free rates were estimated by the Kaplan–Meier method and analyzed by log-rank tests. Statin therapy was initiated for 18 patients and not initiated for 37. There were no significant differences between the groups with or without the initiation of statin therapy in terms of the survival rate ($\chi^2 = 0.11$; $P = 0.7$), renal dysfunction free rate ($\chi^2 = 0.19$; $P = 0.7$), or death/renal dysfunction free rate ($\chi^2 = 0.31$; $P = 0.6$) (figure not shown).

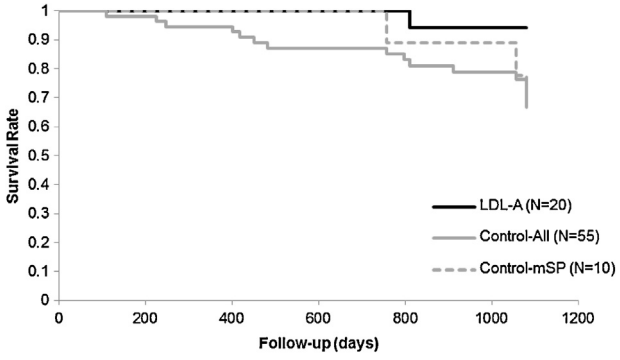


Fig. 1 – Survival rates estimated by Kaplan–Meier analysis and analyzed by log-rank tests. Black line denotes LDL-a (N = 20) and gray line denotes control-All (all; N = 55), and dashed-gray line denotes the cohort with more severe proteinuria, control-mSP (N = 10). Survival rate was significantly higher ($\chi^2 = 4.05$; $P = 0.04$) in LDL-a than control-All.

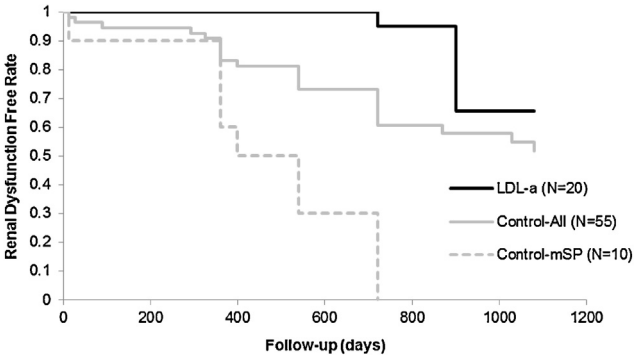


Fig. 2 – Renal dysfunction free rates estimated by Kaplan–Meier analysis and analyzed by log-rank tests. Black line denotes LDL-a (N = 20), gray line denotes control-All (all, N = 55), and dashed-gray line denotes the cohort with more severe proteinuria, control-mSP (N = 10). Renal dysfunction free rate was significantly higher in LDL-a than control-mSP ($\chi^2 = 28.4$; $P < 0.001$).

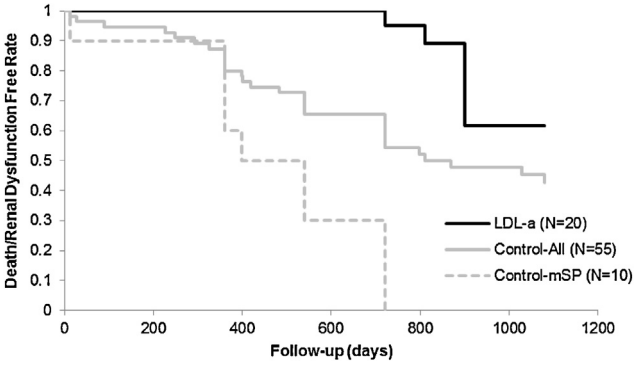


Fig. 3 – Death/renal dysfunction free rates estimated by Kaplan–Meier analysis and analyzed by log-rank tests. Black line denotes LDL-a (N = 20), gray line denotes control-All (all; N = 55), and dashed-gray line denotes the cohort with more severe proteinuria, control-mSP (N = 10). Death/renal dysfunction free rate was significantly higher in LDL-a than control-All ($\chi^2 = 4.50$; $P = 0.03$) and control-mSP ($\chi^2 = 28.02$; $P < 0.001$).

Table 3 – Prognostic factors of severe diabetic nephropathy analyzing control-All cohort.

Variable	Death			Renal dysfunction			Death/renal dysfunction		
	OR	95% CI	P value	OR	95% CI	P value	OR	95% CI	P value
Age	0.86	0.74–1.01	0.06						
BMI	1.35	0.89–2.04	0.1						
Creatinine (serum)				0.97	0.95–1.00	0.06			
Total protein (serum)				6.55	0.51–84.70	0.15	50.0	2.52–989.8	0.01
LDL-cholesterol	0.96	0.93–1.00	0.03	0.93	0.88–0.99	0.03	0.94	0.88–1.00	0.04

4. Discussion

Diabetic nephropathy is a potentially life-threatening condition having a poor prognosis, with a high risk of progression to end-stage renal failure. Although there have been several reports noting short-term recovery of clinical symptoms or parameters with LDL-apheresis therapy, there is insufficient data or evidence about its long-term effects, such as its prognostic effect. In this retrospective study, we followed up patients with severe diabetic nephropathy in the LDL-a and control cohorts and examined the long-term effects of LDL-apheresis.

According to the baseline characteristics and medical history, the disease condition of LDL-a was more severe than control-All, and the condition of control-mSP was more severe than control-All and near that of LDL-a but not at the same level. Despite the difference in the degree of disease severity, survival and the renal dysfunction free and death/renal dysfunction free rates were significantly higher in LDL-a than the control cohorts. Furthermore, LDL-a cohort compared with Reduction in End Points in Noninsulin-Dependent Diabetes Mellitus with the Angiotensin II Antagonist Losartan (RENAAL) study subgroup data (albuminuria >3.0 g/g subgroup; 289 patients) [7]. Baseline data were similar with LDL-a cohort in this study (age: 58.1 ± 7.8 vs. 59.3 ± 13.8, serum creatinine: 2.1 ± 0.5 mg/dL vs. 1.9 ± 0.9 mg/dL as described 170.6 ± 81.3 mol/L in manuscript, eGFR: 33.8 ± 11.0 mL/min/1.73 m^2 vs. 35.1 ± 17.7 mL/min/1.73 m^2, proteinuria: 8.9 ± 4.3 g/day vs. 10.5 ± 2.1 g/day; albuminuria >3.0 g/g subgroup vs. LDL-a cohort, respectively). On the other hand, obvious difference was observed in the prognosis of these cohorts. The death/renal dysfunction (defined as doubling of serum creatinine concentration, chronic hemodialysis initiation, or renal transplantation) rate were probably 60% in albuminuria >3.0 g/g subgroup and 5% in LDL-a cohort for 2 years, and probably 80% in albuminuria >3.0 g/g subgroup and 30% in LDL-a cohort for 3 years, respectively. LDL-a cohort was small, but this comparison result was very impressive and suggested the possibility of LDL apheresis therapy for severe diabetic nephropathy patients.

A survey of the prognostic factors identified LDL-cholesterol as an estimated common independent factor for diabetic nephropathy with severe proteinuria. Furthermore, despite the fact that statin also reduces the serum LDL-cholesterol level, statin administration had no influence on the prognosis. LDL-apheresis is considered to directly focus on the therapeutic target LDL-cholesterol, and may be a promising therapy for diabetic nephropathy with severe proteinuria. On the other hand, although the survival rate was significantly different between LDL-a and control-All, there was no significant difference from the more severe cohort, control-mSP, as noted above. Similarly, despite the fact that LDL-apheresis therapy reduces serum LDL-cholesterol, which is one of the risks for CAD, the incidence of CAD was higher in LDL-a than control-All. These trends are thought to be due to the small size of the LDL-a and control-mSP cohorts. However, statistical analysis confirmed the possibilities which LDL-apheresis contributes to improvement in avoiding death and renal dysfunction in severe diabetic nephropathy patients in the nephrotic syndrome state.

In the pathogenesis of diabetic nephropathy, proteinuria is one of the established risk markers observed for progressive renal function loss [5,6]. Renal function loss is exacerbated by collapse of the glomerular filtration barrier structure. Podocytes, which have a key role in maintaining the integrity of the glomerular filtration barrier, are also a clinically effective marker and linked to the development of proteinuria [9,11,12]. We previously reported that LDL-apheresis effectively reduces podocyte excretion and ameliorates renal dysfunction in patients with nephrotic syndrome caused by diabetic nephropathy, and suggested the possibility that LDL-apheresis maintains renal function by protecting podocytes [17]. Some investigators have reported a relationship between hyper LDL-cholesterolemia and glomerular injury in inflammation [23,24]. With oxidative modifications of the major cholesterol-carrying lipoproteins, the LDLs, the oxidized LDLs are taken up by the scavenger receptor of macrophages, which leads to the formation of foam cells and thrombus, and stimulates monocytes to secrete various cytokines, thus accelerating inflammation [11]. According to the results of several studies showing that LDL-apheresis removes various molecules such as oxidized LDL, TNF-alfa, IL-6, VEGF, and MCP-1, among the inflammatory cytokines or chemokines [16], the clinical efficacy of LDL-apheresis is considered to be exerted by the removal of oxidative/inflammatory molecules and modulation of the inflammatory cascade in the glomerulus. Therefore, LDL-apheresis is a promising therapy that rescues renal function by maintenance of the glomerular basement membrane/podocytes, and contributes to improving the prognosis of diabetic nephropathy with severe proteinuria.

In this study, all patients in the LDL-a cohort received only one course of six to 12 sessions of LDL-apheresis therapy, and drug medication such as statin, ARB, and insulin for diabetic nephropathy were started or continued. Renal function maintenance was higher in LDL-a compared with the control cohorts, and LDL-apheresis therapy actually delayed the

progression of ESRD or initiation of chronic hemodialysis. However, although the renal function maintenance rate remained high until approximately day 900 after LDL-apheresis, the rate then fell slightly in LDL-a. These processes may suggest that LDL-apheresis is a therapy that should be considered not only once, but twice or more times, adjusting the treatment to the patient's condition.

In this study, we found the possibilities which LDL-apheresis contributes to survival extension and renal function maintenance in severe diabetic nephropathy patients. However, this study has some limitations such as retrospective design and performed in one hospital, we think it is not enough as evidence. In the future, a prospective study will be carried out, and we expect to accumulate more evidence to establish the most suitable therapy.

Conflict of interest

The authors declare that they have no conflict of interest.

Disclosure

No sponsors were involved in this retrospective study, and all authors declare that they have no relevant financial interests.

Acknowledgments

The authors thank the staff of Shin-Matsudo Central General Hospital for their important contributions.

No sponsors were involved in this retrospective study, and the authors declare that they have no relevant financial interests.

REFERENCES

[1] Ritz E, Rychlík I, Locatelli F, Halimi S. End-stage renal failure in type 2 diabetes: a medical catastrophe of worldwide dimensions. Am J Kidney Dis 1999;34:795–808.
[2] Atkins RC, Briganti EM, Lewis JB, Hunsicker LG, Braden G, Champion de Crespigny PJ, et al. Proteinuria reduction and progression to renal failure in patients with type 2 diabetes mellitus and overt nephropathy. Am J Kidney Dis 2005;45:281–7.
[3] Sarnak MJ, Jaber BL. Mortality caused by sepsis in patients with end-stage renal disease compared with the general population. Kidney Int 2000;58:1758–64.
[4] Byrne C, Vernon P, Cohen JJ. Effect of age and diagnosis on survival of older patients beginning chronic dialysis. J Am Med Assoc 1994;271:34–6.
[5] Parving HH. Diabetic nephropathy: prevention and treatment. Kidney Int 2001;60:2041–55.
[6] Remuzzi G, Schieppati A, Ruggenenti P. Nephropathy in patients with type 2 diabetes. N Engl J Med 2002;346:1145–51.
[7] de Zeeuw D, Remuzzi G, Parving HH, Keane WF, Zhang Z, Shahinfar S, et al. Proteinuria, a target for renoprotection in patients with type 2 diabetic nephropathy: lessons from RENAAL. Kidney Int 2004;65:2309–20.
[8] Brenner BM, Cooper ME, de Zeeuw D, Keane WF, Mitch WE, Parving HH, et al. RENAAL Study Investigators: effects of Losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. N Engl J Med 2001;345:861–9.
[9] Muso E, Yashiro M, Matsushima M, Yoshida H, Sawanishi K, Sasayama S. Does LDL-apheresis in steroid-resistant nephrotic syndrome affect prognosis? Nephrol Dial Transplant 1994;9:257–64.
[10] Kobayashi S. LDL-apheresis for diabetic nephropathy: a possible new tool. Nephron 1998;79:505–6.
[11] Cattin L, Petrucco A, Cazzolato G, Bon GB, Borelli V, Nardon E, et al. Low density lipoprotein-apheresis decreases oxidized low density lipoproteins and monocyte adhesion to endothelial cells. ASAIO J 1997;43:209–13.
[12] Sampietro T, Tuoni M, Ferdeghini M, Ciardi A, Marraccini P, Prontera C, et al. Plasma cholesterol regulates soluble cell adhesion molecule expression in familial hypercholesterolemia. Circulation 1997;96:1381–5.
[13] Nakamura T, Kawagoe Y, Matsuda T, Takahashi Y, Sekizuka K, Ebihara I, et al. Effect of LDL apheresis and vitamin E-modified membrane on carotid atherosclerosis in hemodialyzed patients with arteriosclerosis obliterans. Kidney Blood Press Res 2003;26:185–91.
[14] Kobayashi S, Moriya H, Maesato K, Okamoto K, Ohtake T. LDL-apheresis improves peripheral arterial occlusive disease with an implication for anti-inflammatory effects. J Clin Apher 2005;20:239–43.
[15] Stefanutti C, Vivenzio A, Di Giacomo S, Ferraro PM. Cytokines profile in serum of homozygous familial hypercholesterolemia is changed by LDL-apheresis. Cytokine 2011;55:245–50.
[16] Stefanutti C, Morozzi G, Petta A. Lipid and low-density-lipoprotein apheresis: effects on plasma inflammatory profile and on cytokine pattern in patients with severe dyslipidemia. Cytokine 2011;56:842–9.
[17] Nakamura T, Kawagoe Y, Ogawa H, Ueda Y, Hara M, Shimada N, et al. Effect of low-density lipoprotein apheresis on urinary protein and podocyte excretion in patients with nephrotic syndrome due to diabetic nephropathy. Am J Kidney Dis 2005;45:48–53.
[18] Pagtalunan ME, Miller PL, Jumping-Eagle S, Nelson RG, Myers BD, Rennke HG, et al. Podocyte loss and progressive glomerular injury in type II diabetes. J Clin Invest 1997;99:342–8.
[19] Nakamura T, Ushiyama C, Shimada N, Sekizuka K, Ebihara I, Hara M, et al. Effect of the antiplatelet drug dilazep dihydrochloride on urinary podocytes in patients in the early stage of diabetic nephropathy. Diabetes Care 2000;23:1168–71.
[20] Hara M, Yanagihara T, Kihara I. Urinary podocytes in primary focal segmental glomerulosclerosis. Nephron 2001;89:342–7.
[21] Jennete JC, Olson JL, Schwartz MM, Silva FG, editors. Heptinstall's pathology of the kidney. 6th ed. Philadelphia: Lippincott Williams & Wilkins; 2006.
[22] Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. J Am Stat Assoc 1958;53:457–81.
[23] Kamijo Y, Kaneko Y, Ichikawa T, Kobayashi N, Koyama T, Kakegawa T, et al. A case of nephrotic syndrome due to lupus nephritis which was controlled with low-density lipoprotein apheresis. Ther Apheresis 2002;6:459–62.
[24] Schlondoff D. Cellular mechanisms of lipid injury in the glomerulus. Am J Kidney Dis 1993;22:72–82.